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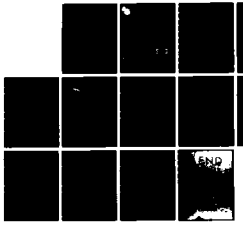

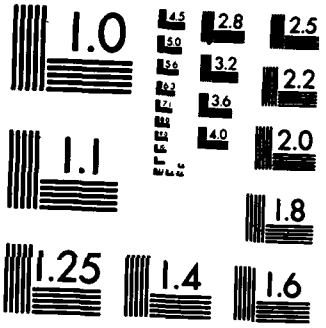
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INSTITUTE REPORT NO. 186

FATAL HEMORRHAGIC SHOCK: THE SUPERIORITY OF COMPATIBLE FRESH FROZEN PLASMA AS A RESUSCITATION AGENT

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Fatal Hemorrhagic Shock: The Superiority of Compatible Fresh Frozen Plasma as a Resuscitation Agent--Traverso et al

In conducting the research described in this report, the investigation adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Revision of the Guide for Laboratory Animal Facilities and Care, Institute of Laboratory Animal Resources, National Research Council.

This material has been reviewed by Letterman Army Institute of Research and there is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. *(AR 360-5)*

(signed) Thomas F. Zuck, COL MC 20 August 1984
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ABSTRACT

We developed a fixed-volume porcine hemorrhage model that simulates the rapid exsanguination of combat or civilian trauma victims. In this study we compared the ability of five resuscitation solutions to prevent death after an otherwise lethal hemorrhage in 100 swine. The shed blood was replaced in a 1:1 ratio with either autologous whole blood (WB), untyped swine-fresh frozen plasma (FFP), typed FFP, 5 percent human serum albumin (ALB), or normal saline (NS). Survival rate analysis indicated that WB was significantly better than FFP (untyped), ALB, or NS but not better than typed FFP. The 24-hour survival rates were: WB = 90%, typed FFP = 79%, untyped FFP = 56%, ALB = 57%, and NS = 25%. All deaths in the untyped FFP group suddenly occurred during or within 15 minutes after treatment in a recovering animal. Deaths in the ALB group steadily occurred for up to 150 minutes after treatment. Analysis of hemodynamic, arterial blood gas, and acid-base data indicated that WB and FFP provided a better acid buffering capacity in surviving animals than NS or ALB. We conclude that compatible FFP is a better resuscitation agent than ALB after an otherwise fatal hemorrhage because FFP is a better acid buffer.

ABSTRACT

We developed a fixed-volume porcine hemorrhage model that simulates the rapid exsanguination of combat or civilian trauma victims. In this study we compared the ability of five resuscitation solutions to prevent death after an otherwise lethal hemorrhage in 100 swine. The shed blood was replaced in a 1:1 ratio with either autologous whole blood (WB), untyped swine-fresh frozen plasma (FFP), typed FFP, 5 percent human serum albumin (ALB), or normal saline (NS). Survival rate analysis indicated that WB was significantly better than FFP (untyped), ALB, or NS but not better than typed FFP. The 24-hour survival rates were: WB = 90%, typed FFP = 79%, untyped FFP = 56%, ALB = 57%, and NS = 25%. All deaths in the untyped FFP group suddenly occurred during or within 15 minutes after treatment in a recovering animal. Deaths in the ALB group steadily occurred for up to 150 minutes after treatment. Analysis of hemodynamic, arterial blood gas, and acid-base data indicated that WB and FFP provided a better acid buffering capacity in surviving animals than NS or ALB. We conclude that compatible FFP is a better resuscitation agent than ALB after an otherwise fatal hemorrhage because FFP is a better acid buffer.

Key Words: hemorrhage, shock, plasma, albumin and swine.

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TABLE OF CONTENTS

FATAL HEMORRHAGIC SHOCK: THE SUPERIORITY OF COMPATIBLE FRESH FROZEN PLASMA AS A RESUCITATION AGENT

Hemorrhagic shock following rapid exsanguination occurs frequently in civilian and combat injuries. One-half of civilian trauma deaths occur within an hour of injury from exsanguination or central nervous system trauma (1). Another 30 percent of civilian trauma deaths occur within 2 to 3 hours; these deaths are due to major internal hemorrhage (1). Of the 43,601 hostile action deaths in Vietnam (between 1 January 1961 and 31 December 1975), 88 percent died before receiving medical care (2). According to Bellamy (3), 50 percent of those soldiers killed in action in Vietnam died of rapid hemorrhage. Among the combat casualties who "died of wounds" in a hospital, the most common cause of death was head injury (42%), and the next highest number of deaths (24%) resulted from hemorrhagic shock (4).

Since rapid hemorrhage is prevalent in civilian and combat trauma, methods of treatment are still important issues. Hemorrhage control is the basis for effective treatment. Early fluid replacement is required. Which fluid to use in the early resuscitation period, when blood is not available, is an extremely important question. The controversy of crystalloid versus colloid solutions in resuscitation is well known (5). Both types of solutions are effective but, because of the large volumes required with crystalloid solutions (6) and the logistical problems of carrying the increased weight on the battlefield, colloid solutions may have an advantage in potentially fatal rapid hemorrhage.

Our study was designed to survey conventional colloid resuscitation fluids (oncotic activity with or without oxygen carrying ability) in the treatment of otherwise fatal rapid exsanguination. We developed a porcine fixed-volume hemorrhage model to simulate the hemorrhage-to-death time of the untreated human trauma exsanguination victim (7). This unanesthetized and unheparinized swine model is 100 percent fatal if untreated. The results of this study reflect assessment of treatment during a rigidly controlled hypovolemic condition, not compounded by the extra experimental variable of tissue trauma. However, even in the absence of direct tissue injury, survival time in this experimental model is similar to the interval observed during fatal rapid exsanguination seen in human trauma and is much shorter than the purposely extended survival time of the commonly utilized fixed-pressure, heparinized, and anesthetized "Wigger's" model (8).

We found that compatible fresh-frozen plasma and autologous whole blood provided the best survival results over equal volumes of untyped, randomly used fresh-frozen plasma or 5 percent human serum albumin in normal saline.

MATERIALS AND METHODS

Surgical Placement of Hemorrhage and Treatment Catheters. Immature female swine between 15 and 24 kg were anesthetized with endotracheal halothane 5 days before hemorrhage. All surgical procedures were done by the same investigator (LWT). Under sterile conditions and using a left retroperitoneal dissection, a polyvinylchloride catheter (OD=3.7 mm, ID=2.6 mm) was placed as a sideport in the infrarenal aorta and anchored in place via a polyester patch cemented to the catheter (Fig. 1).

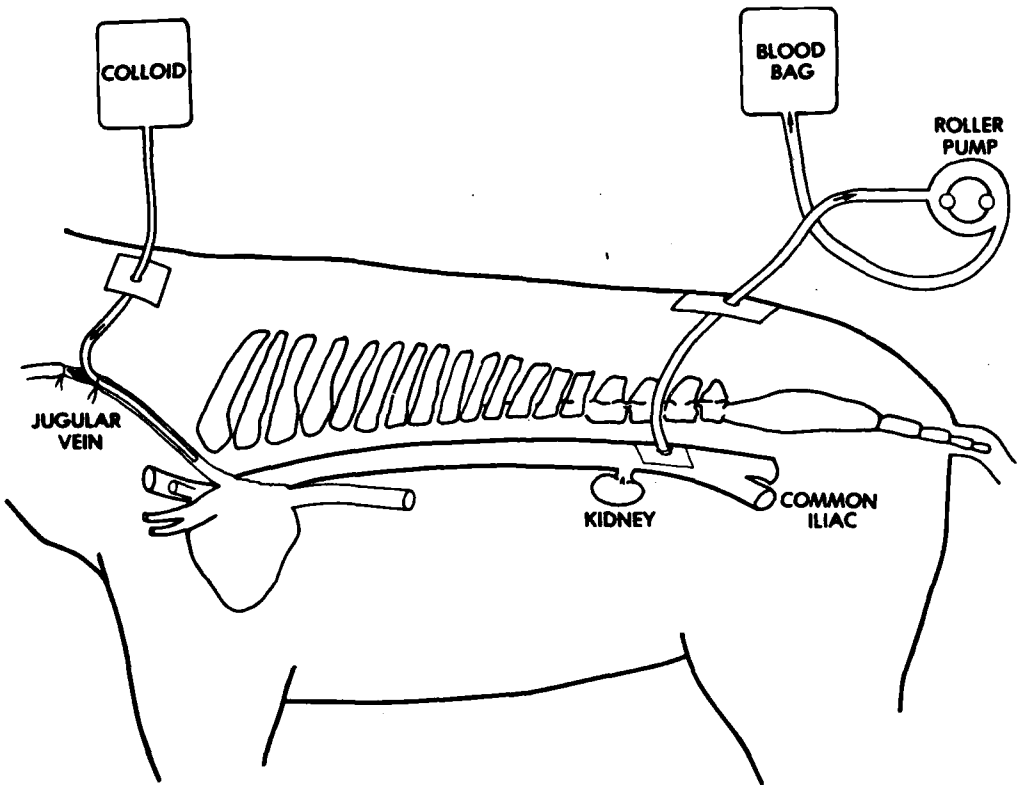

Figure 1. The distal aortic sideport catheter and central venous treatment catheter are shown in this unheparinized and unanesthetized hemorrhage model.

The intravascular end of the catheter was previously cut to be flush with the inner aortic wall. If the intravascular portion of the catheter extended into the aortic lumen for more than a millimeter, turbulence resulted in clot formation around the catheter. The result would be catheter malfunction even with prior heparin flushing. The retroperitoneal catheter was tunnelled medial to the paraspinal muscles, and exited the skin in the midline lumbar area. The catheter was anchored to the skin with nylon suture and then covered with a double layer Velcro patch which was also sutured to the skin. The aortic sideport increased our ability to exsanguinate unheparinized swine rapidly and our success rate increased from 81 percent to 95 percent in the last 229 swine (9). An intravenous treatment catheter of polyvinylchloride (OD=2.8 mm, ID=1.8 mm) was threaded into a supra-atrial position via the left external jugular vein and a neck incision. The catheter was tunnelled to exit the skin in the midline cervical area, sutured to the skin, and also protected with a Velcro patch. At the end of the surgical procedure, both catheters were filled with 2 ml of sterile unheparinized saline, containing 40 mg of gentamicin. The catheters were not disturbed again until the day of hemorrhage.

Hemorrhage and Treatment Methods. All swine (n=100) had 54 ml/kg of blood removed in 15±2 minutes as previously described (7). The hemorrhage catheter was attached to a roller pump (Model 610, Bio Rad Laboratories, Richmond, CA) with a pump tubing of silicone rubber (OD=5.0 mm, ID=1.75 mm). The rate of hemorrhage was adjusted by measuring the weight of blood collection bags or the volume of pump effluent in a graduated cylinder. Starting within 4 minutes after the end of hemorrhage, the shed blood was replaced over 30 minutes by an equal volume oftreatment fluid given through the intravenous catheter. Treatment after hemorrhage avoided the experimental variable of losing treatment solution during hemorrhage. The hemorrhage time, treatment type, treatment time, and prehemorrhage weight of the swine were recorded. Survival of the animal was then observed with death defined as apnea and unresponsiveness to stimuli. A survivor was defined as a swine that lived for 24 hours.

Functional Measurements. Hemodynamic control measurements and arterial blood samples were obtained just prior to hemorrhage, at the end of hemorrhage (zero-time), and then at intervals after hemorrhage depending on survival: 15 and 30 minutes, hourly at 1 through 6 hours, and 24 hours. At each of these times, mean aortic pressure (AP) and heart rate (HR) were obtained with a transducer (Statham Instruments, Inc., Model P23Db, Oxnard, CA) and a recorder (Gould Brush 2000, Gould, Inc., Cleveland, OH). Arterial blood samples were obtained at the above times for pH, pO_2, pCO_2, and bicarbonate (HCO_3) (Model 813 pH/Blood Gas Analyzer, Instrumentation Laboratory, Lexington, MA). Arterial blood was also sampled for hematocrit (Hct) and serum lactate (Sigma Technical Bulletin No. 7261-UV).

Treatment Groups. The treatment type and abbreviation, number of animals in each group, and treatment times are listed in Table 1. Treatments were chosen at random on a daily basis over a 10-month period, except for the compatible fresh-frozen plasma (FFPx) experiments which were studied at random during the last 4 months of the study.

Table 1: Experimental Design

Group	Fluid*	No. Used (n)	Treatment Time (min)	Survivors Autopsied
NS	Normal Saline	20	20±2†	1
ALB	5% Albumin in NS	21	30±3	4
FFP	Fresh Frozen Plasma‡	25	30±3	3
FFPx	Crossmatched FFP	14	30±3	3
WB	Autologous Fresh Whole Blood	20	30±3	2

* 100% of the shed blood was replaced.
† If treatment time = 30 min, many animals would die during treatment with NS.
‡ Not typed.

The average pH, osmolarity, and electrolyte concentration of each solution were derived from the manufacturer's description or measured by the authors. Normal saline (NS) was commercially obtained (Travenol Labs, Inc., Deerfield, IL, lot number: 5C869R8). Colloidal solutions were obtained from varied sources: 5 percent human serum albumin (ALB) in NS (Armour Pharmaceuticals Co., Kankakee, IL, lot number: W18408); and fresh-frozen plasma (FFP) from swine. The FFP was obtained from the first unit of blood removed from other swine in this study and prepared according to the method of the Technical Manual of the American Association of Blood Banks (7th ed., 1977). In addition, all FFP units were used within 1 month of collection and cultured for bacteria before freezing. Any unit associated with bacterial growth by culture was excluded. For the FFPx treatment group, FFP was typed against washed erythrocytes obtained at random from ten to twelve healthy swine. FFP (0.05 ml) was combined with an

equal volume of donor erythrocytes at 4, 22, and 37°C for 30 minutes. The mixture was observed for hemolysis and agglutination of cells after centrifugation for 30 seconds. In our experience approximately 20 to 30 percent of swine FFP donors would not hemolyze or agglutinate other swine erythrocytes and these "universal plasma donors" were the swine plasma source for the FFPx group. Whole blood units were collected in commercially prepared blood bags, containing a solution of citrate-phosphate-dextrose-adenine (CPDA-1) (Cutter Laboratories, Berkeley, CA).

Autopsy Studies. Swine living for 24 hours after hemorrhage i.e., survivors, received a standard euthanasia solution. However, one or more survivors in each treatment group were not euthanized until 3 days after treatment and were then autopsied (Table 1). The histology of the following tissues was examined: hippocampus and adjacent cerebrum (bilateral), midbrain, cerebellum (bilateral), brain stem and cervical spinal cord, pituitary gland, adrenal gland, lung (bilateral), heart, rectus abdominus muscle, diaphragm, liver, kidney (bilateral), pancreas, stomach, and terminal ileum. In addition, a random unoperated swine from the same animal colony served as a control.

Data Management and Statistics. For each swine, all data were recorded in a data base management record. The swine weight and all of the blood and hemodynamic data were analyzed at each time period with a one-way analysis of variance (ANOVA). If a significant F ratio was found, then a multiple comparison (Bonferroni t-test) was performed to determine significant differences among treatment groups. Survival during the 24-hour observation period was studied with life table analysis according to the method of Mantel (10). Significant differences to reject a null hypothesis were defined, a priori, with $P<0.05$ for functional measurement interval data and $P<0.10$ for survival data.

RESULTS

The average pH, osmolarity, and electrolyte concentration for each resuscitation solution are shown in Table 2.

Table 2: Resuscitation Solution Data

Fluid	n	pH	mOsm/l	Na	K	Cl	Ca	Mg	HCO_3
				<-------------mEq/l---------->					
Normal Saline*		5.0	308	154	...	154	...	...	...
5% Albumin in Normal Saline	3	6.7	290	147	...	118	2.5	...	...
Fresh Frozen Plasma (CPDA-1)	16	7.2	305	163	3.5	82	8.2	1.2	23
Whole Blood (CPDA-1)	6	7.2	285	158	4.6	85	8.5	1.6	20

n = number of measurements made by authors
* = published values by the manufacturer

A significant difference was not seen among the mean weights (kg$\pm$S.D.) of the swine of each treatment group: NS = 20.0$\pm$2.0, ALB = 19.5$\pm$2.2, FFP = 20.4$\pm$2.5, FFPx = 21.0$\pm$1.8, and WB = 19.2$\pm$2.9.

A comparison of survival rates after 100% replacement of the shed blood by the various solutions is shown in Figure 2. The Mantel-Cox statistic indicated significant differences were present when the survival curves of the treatment groups were compared: WB was significantly better than ALB ($P = 0.024$), FFP ($P = 0.015$), and NS ($P = 0.001$) but WB survival was not different than FFPx survival ($P = 0.377$).

Blood and hemodynamic data for the treatment groups are summarized graphically in Figure 3(A through E). The numeric data and ANOVA results are listed in Tables 3 and 4. In Figure 3A the NS treatment group was associated with the lowest AP from the 15 to 120-minute intervals while HR values in the NS group were similar to the WB group until the 300-minute period when tachycardia was seen in all groups as compared to WB. Tachycardia was seen with the ALB, FFP, and FFPx groups after the 60-minute period. Volume expansion associated with asanguinous fluids was reflected after the 15-minute period by a significantly lower Hct in the ALB, FFP, and, FFPx groups (Figure 3B). The Hct for the NS group was significantly higher than the Hct for the asanguinous colloid solutions. Lactate values were persistently

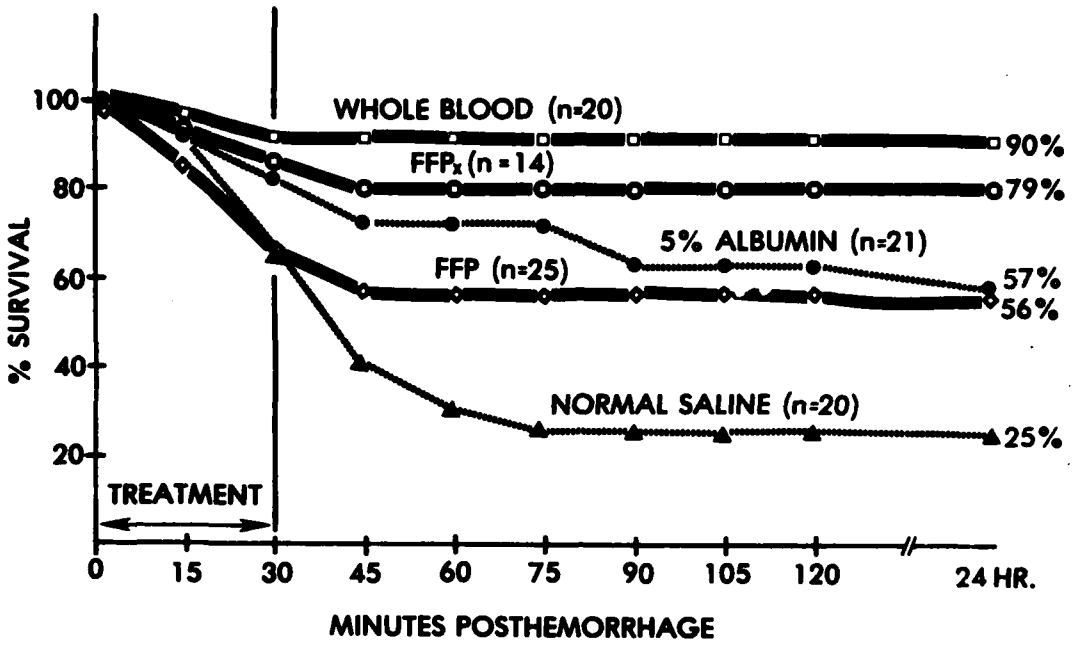

Figure 2. The percent survival over time in minutes after hemorrhage is shown for the 100% replacements of shed blood over 30 minutes. Significant differences ($P < 0.05$) are present between WB vs ALB, FFP, and NS but not WB vs FFPx.

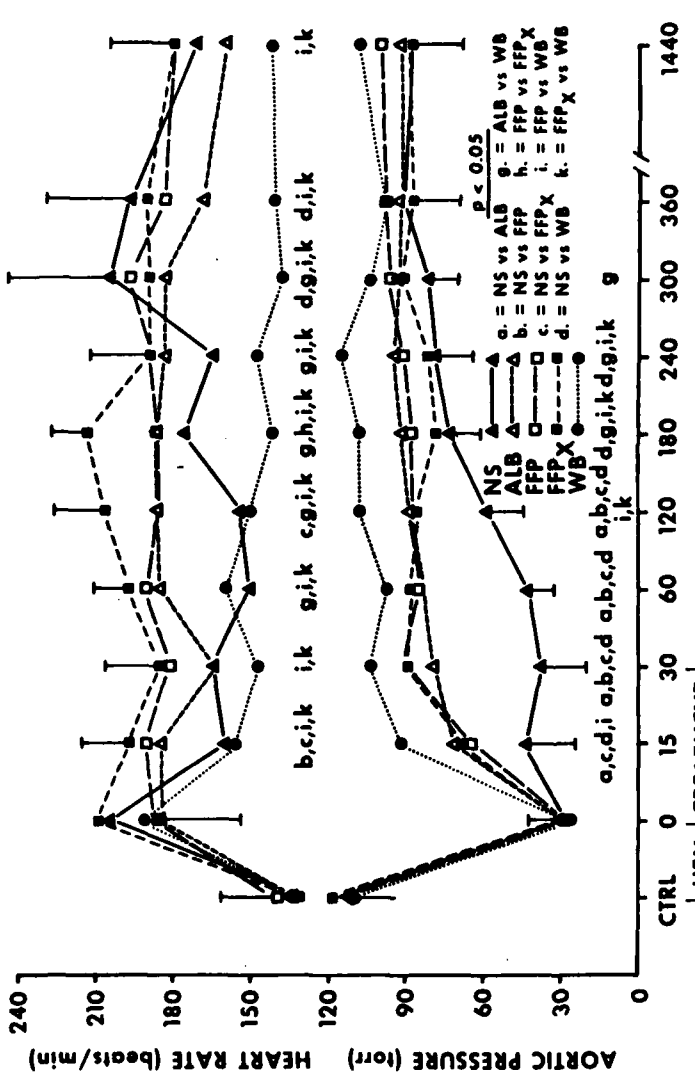

Figure 3A. The change in aortic pressure and heart rate from the before hemorrhage control value (CTRL), the end of hemorrhage (0 time), and then in minutes after hemorrhage. *HEM* = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the multiple lines. Significant ANOVA results are depicted on the graph.

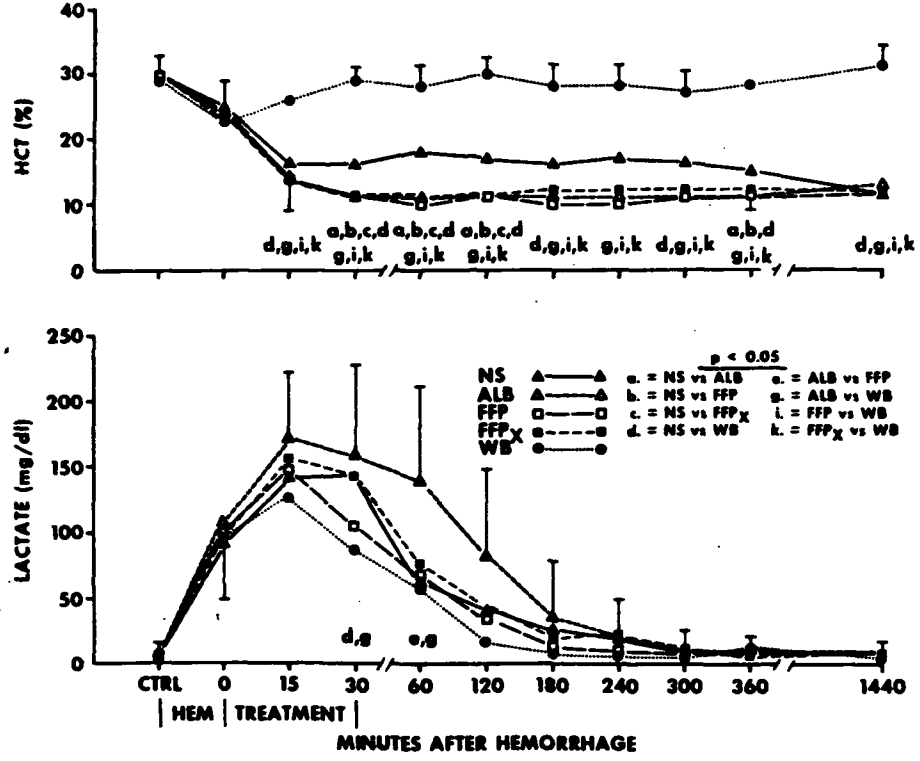

Figure 3B. The change in lactate and Hct from the before hemorrhage control value (CTRL), the end of hemorrhage (0 time), and then in minutes after hemorrhage. HEM = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the multiple lines. Significant ANOVA results are depicted on the graph.

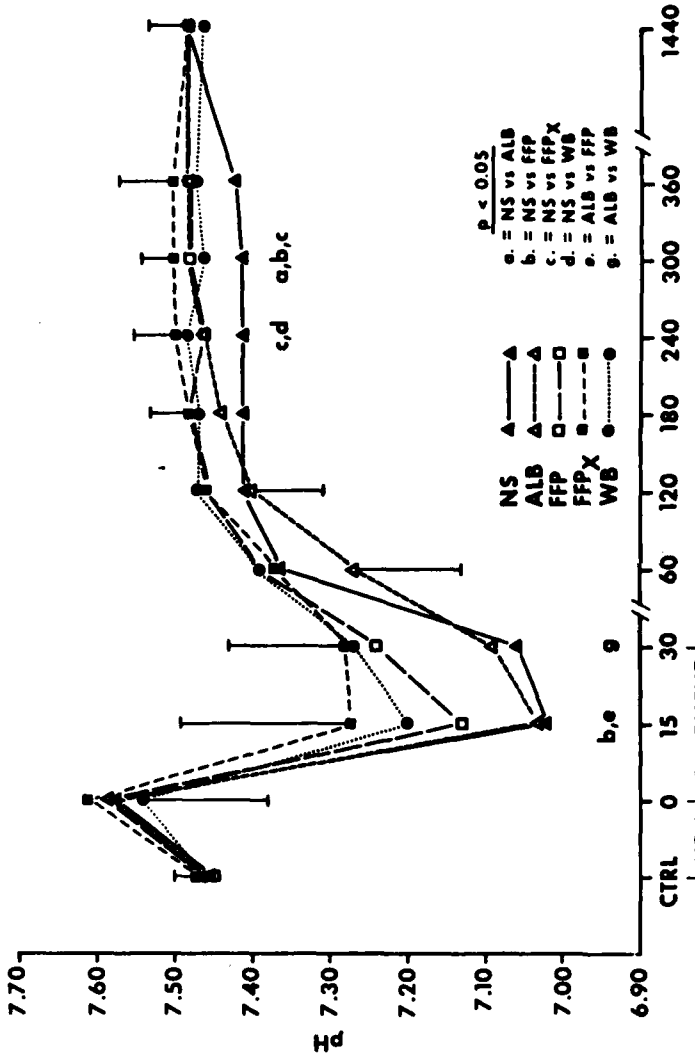

Figure 3C. The change in pH from the before hemorrhage control value (CTRL), the end of hemorrhage (0 time), and then in minutes after hemorrhage. HEM = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the multiple lines. Significant ANOVA results are depicted on the graph.

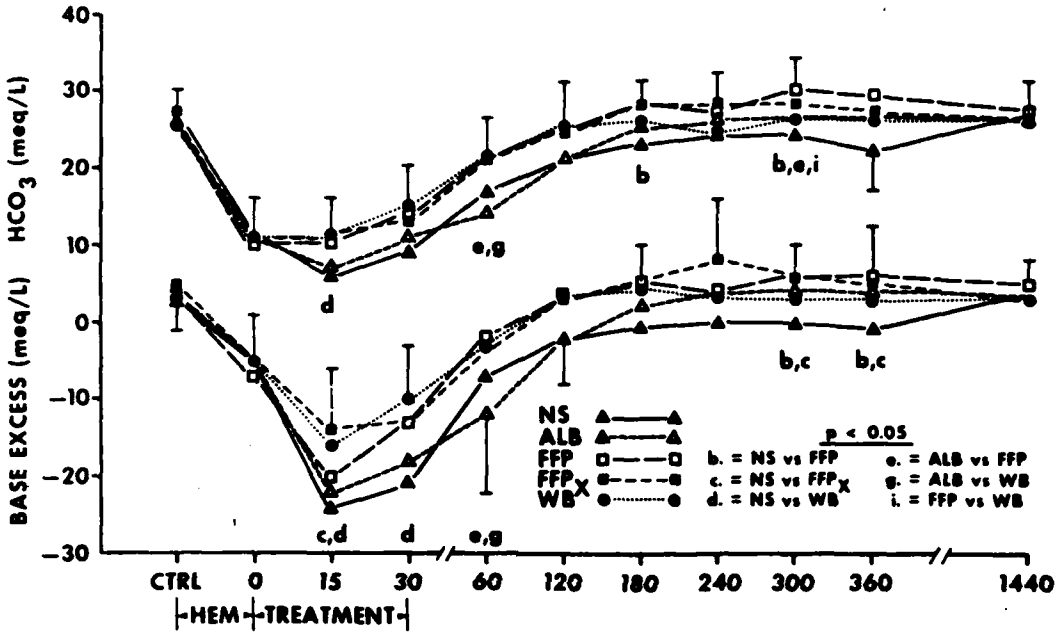

Figure 3D. The change in BE and HCO_3 from the before hemorrhage control value (CTRL), the end of hemorrhage (0 time), and then in minutes after hemorrhage. HEM = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the multiple lines. Significant ANOVA results are depicted on the graph.

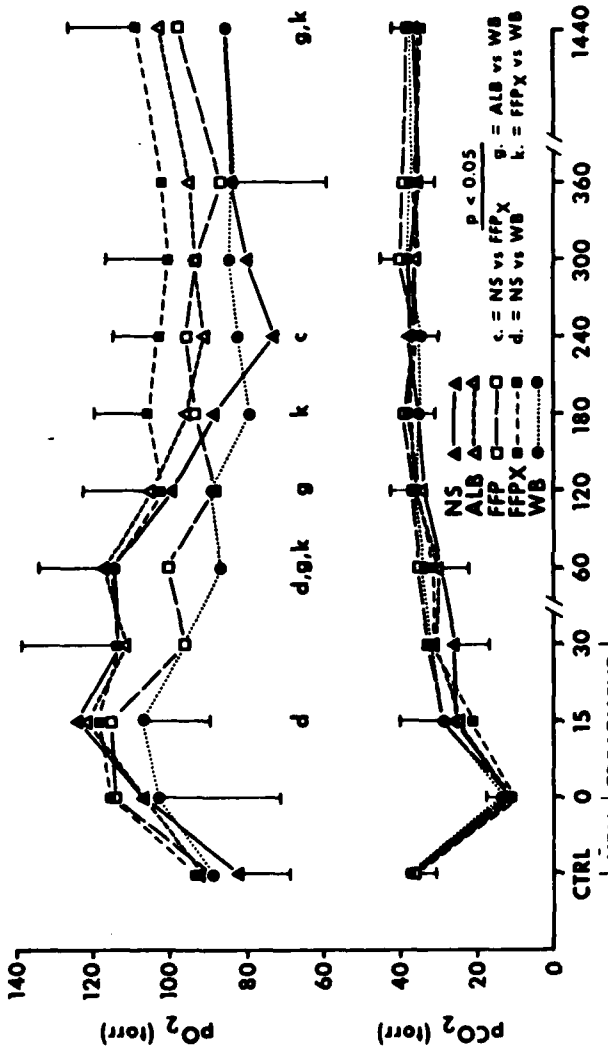

Figure 3E. The change in pCO_2 and O_2 from the before hemorrhage control value (CTRL), the end of hemorrhage (0 time), and then in minutes after hemorrhage. HEM = hemorrhage. Representative standard deviations are shown to avoid obscuring the course of the multiple lines. Significant ANOVA results are depicted on the graph.

Table 3: Arterial Blood Gas Data (Mean ± Standard Deviation)

FLUID	CTRL	MINUTES AFTER HEMORRHAGE 0	15	30	60	120	180	240	300	360	1440
pH											
NS	7.46±.03	7.59±.10	7.02±.17	7.06±.26	7.36±.08	7.41±.06	7.41±.04	7.41±.03	7.41±.03	7.42±.06	7.48±.04
ALB	7.47±.03	7.58±.14	7.03±.18	7.09±.22	7.27±.14	7.40±.09	7.44±.06	7.46±.03	7.48±.03	7.48±.03	7.48±.02
FFP	7.45±.04	7.58±.12	7.13±.20	7.24±.13	7.39±.06	7.46±.06	7.48±.04	7.46±.04	7.48±.04	7.48±.05	7.48±.03
FFPx	7.47±.03	7.61±.08	7.27±.22	7.28±.15	7.37±.12	7.46±.06	7.48±.05	7.50±.05	7.50±.04	7.50±.07	7.48±.05
WB	7.46±.04	7.54±.16	7.20±.13 *b,e*	7.27±.12 *g*	7.39±.08	7.47±.04	7.47±.03	7.48±.04 *c,d*	7.46±.02 *a,b,c*	7.47±.03	7.46±.04
pCO_2 (Torr)											
NS	38±4	12±4	26±7	26±9	29±6	34±4	36±4	38±6	38±5	35±6	36±3
ALB	38±3	12±4	25±7	31±6	30±8	36±5	37±4	37±5	36±5	36±5	36±2
FFP	37±3	11±4	29±11	33±6	35±6	37±5	39±3	37±5	40±5	39±5	38±4
FFPx	36±5	11±4	21±7	31±5	31±3	35±4	38±2	36±4	36±3	36±2	34±2
WB	38±3	13±5	29±6	32±5	34±4	36±4	35±4	35±5	38±4	37±2	37±4 *f,h,k*
pO_2 (Torr)											
NS	82±13	107±22	124±11	113±25	115±17	99±7	88±19	73±14	79±14	84±16	85±26
ALB	92±13	107±20	121±16	111±21	117±15	104±10	95±16	90±20	93±18	94±21	102±9
FFP	89±14	114±16	115±17	95±23	100±29	88±23	93±23	95±14	92±16	86±19	97±28
FFPx	93±12	115±22	118±19	113±18	115±19	102±20	105±14	102±12	99±17	101±12	108±8
WB	89±16	103±31	107±12 *d*	96±21	86±21 *d,g,k*	89±14 *g*	79±16 *k*	82±17 *c*	84±16	83±24	85±14 *g,k*
HCO_3 (meq/l)											
NS	26±4	12±4	6±2	9±6	17±6	21±5	23±3	24±4	24±2	22±5	27±3
ALB	26±5	11±3	7±3	11±6	14±7	21±6	25±4	26±4	26±3	26±2	26±2
FFP	26±3	10±3	10±4	14±6	21±5	25±6	28±3	27±5	30±4	29±4	27±4
FFPx	27±3	11±3	11±5	13±6	21±5	25±4	28±3	28±4	28±2	27±3	26±3
WB	26±3	11±4	11±5 *d*	15±5	21±5 *e,g*	25±4	26±2 *b*	24±6	26±3 *b,e,i*	26±2	26±4
BE (meq/l)											
NS	3±3	-5±5	-24±7	-21±10	-7±7	-2±5	-1±3	0±4	0±1	-1±6	4±3
ALB	3±4	-5±5	-22±7	-18±10	-12±10	-2±6	2±4	4±2	4±2	4±2	4±1
FFP	3±4	-7±5	-20±8	-13±8	-2±6	3±6	5±5	4±6	6±4	6±4	5±3
FFPx	5±3	-5±3	-14±8	-13±10	-4±7	3±4	5±4	8±8	6±3	5±4	3±3
WB	3±3	-5±6	-16±7 *c,d*	-10±7 *d*	-3±6 *e,g*	3±4	4±3	3±4	3±3 *b,c*	3±2 *b,c*	3±3

CTRL=Control

a=NS vs ALB
b=NS vs FFP
c=NS vs FFPx
d=NS vs WB
e=ALB vs FFP
f=ALB vs FFPx
g=ALB vs WB
h=FFP vs FFPx
i=FFP vs WB
k=FFPx vs WB

Table 4: Lactate, Hematocrit, Aortic Pressure, and Heart Rate Data (Mean ± Standard Deviation)

		MINUTES AFTER HEMORRHAGE								
FLUID	CTRL	0	15	30	60	120	180	240	300	360	1440
Lactate (mg/dl)											
NS	7±4	92±44	143±53	143±45	62±33	41±30	27±16	21±9	9±4	13±7	6±1
ALB	9±7	110±31	171±51	158±68	140±72	83±66	38±41	23±22	14±12	10±9	11±7
FFP	8±7	103±31	148±55	105±27	69±18	34±37	14±12	10±3	8±2	8±2	9±3
FFPx	6±2	99±36	157±64	144±69	77±36	45±34	21±15	24±26	14±7	6±2	10±8
WB	7±5	97±32	126±32	88±28 d,g	58±36 e,g	17±13	9±5	7±3	6±1	12±10	6±2
Hematocrit (%)											
NS	30±3	25±4	16±3	16±4	18±3	17±2	16±3	17±5	16±3	15±2	12±2
ALB	29±3	24±2	14±3	11±2	11±2	11±1	11±1	11±1	11±1	11±2	13±2
FFP	30±3	24±3	14±5	11±2	10±2	11±1	10±2	10±1	11±2	11±2	12±2
FFPx	30±2	23±3	14±2	11±2	11±1		12±2	12±2	12±2	12±2	12±3
WB	29±3	23±3	26±4 d,g, i,k	29±2 a,b,c, d,g,i,k	28±3 a,b,c, d,g,i,k	30±2 a,b,c, d,g,i,k	28±3 d,g, i,k	28±3 g,i,k	27±3 d,g, i,k	28±2 a,b,d, g,i,k	31±3 d,g, i,k
Aortic Pressure (Torr)											
NS	112±11	27±9	44±19	38±18	43±10	59±14	73±8	80±16	81±11	91±4	88±11
ALB	115±10	30±10	72±25	80±25	83±16	89±10	92±8	95±9	92±9	91±9	92±8
FFP	116±9	29±9	65±24	91±16	85±11	88±16	88±14	91±21	96±13	98±11	99±14
FFPx	117±12	32±11	69±22	90±18	88±14	86±11	78±17	81±19	92±21	87±18	88±20
WB	110±16	26±8	92±25 a,c, d,i	104±18 a,b, c,d	97±17 a,b, c,d	108±20 a,b,c, d,i,k	108±13 d,g, i,k	115±14 d,g, i,k	104±10 g	97±11	108±18 j
Heart Rate (beats/min)											
NS	135±17	204±27	160±35	164±41	150±29	154±34	176±42	164±20	204±39	196±39	170±21
ALB	134±22	184±30	184±25	163±16	185±14	186±16	186±23	182±15	182±13	167±13	158±29
FFP	140±22	186±26	190±26	181±16	190±14	185±12	186±11	188±16	196±16	182±11	178±25
FFPx	131±16	209±23	197±18	185±21	197±13	205±20	213±14	188±24	188±16	188±31	178±23
WB	133±21	191±30	156±29 b,c, i,k	147±20 i,k	159±29 g,i,k	150±30 c,g, i,k	142±24 g,h, i,k	147±20 g,i,k	137±20 d,g, i,k	140±28 d,i,k	142±39 i,k

CTRL=Control

a=NS vs ALB
b=NS vs FFP
c=NS vs FFPx
d=NS vs WB
e=ALB vs FFP
f=ALB vs FFPx
g=ALB vs WB
h=FFP vs FFPx
i=FFP vs WB
k=FFPx vs WB

elevated in the ALB treatment group versus the other groups and were significantly elevated over the WB group at the 30- and 60-minute periods. In Figure 3C and 3D after NS and ALB treatments the pH, HCO_3, and BE values grouped lower than the FFP, FFPx, and WB groups. After the 120-minute period, the acid-base data of the ALB group coincided closely with the data from the FFP, FFPx, and WB groups rather than the NS group. In Figure 3E, between-group differences were not observed in pCO_2 while the pO_2 values after WB and FFP grouped lower than FFPx, ALB, and NS from the 15- to 120-minute periods. Not all of these differences were consistently significant. The surviving swine at 24 hours after hemorrhage also showed a significantly lower pO_2 in the WB versus the FFPx or ALB groups.sp001

Regardless of the treatment, neither gross nor microscopic differences were found between any of the tissues examined in the surviving animals at autopsy 3 days after hemorrhage. In addition the tissues from the control swine did not differ grossly or histologically from the tissues of the treatment group.

DISCUSSION

The objective of this study was to evaluate colloid solutions (ALB, FFP, and FFPx) in an animal model that simulated the clinical entity of human hemorrhage following trauma. The model was calibrated with simultaneous negative and positive control treatment groups (NS and WB).

The swine weights were not different between treatment groups. Constant weights are especially important when estimating blood volume by weight for fixed-volume removal. Our experience has shown that, regardless of treatment, most animals less than 14 kg will survive while most swine over 25 kg will die after this hemorrhage protocol. Rigid adherence to the weight range of this study is mandatory to achieve reproducibility in the volume of blood removed instead of relying on formulas to estimate blood volume over a wide range of weights.

The 90 percent survival rate after WB includes 2 deaths during treatment which are due to an inherent mortality rate of the rapid hemorrhage of this model. Because of the severe hemorrhage, the survival rates will err on the side of mortality rather than survival. Therefore the survival data could be considered falsely low but not falsely elevated. The model is calibrated with WB and NS. These treatments bracket the extremes in survival and functional measurements. WB and NS treatments resulted in significantly different survival curves. This provides a positive and negative control so that the model's response to the three remaining colloid treatments (FFP, FFPx, and ALB) can be assessed easily. Only FFPx exhibited a survival curve not statistically different from WB. The survival rates were equal for FFP and ALB at 24 hours after hemorrhage. All of the FFP deaths occurred in less than 45 minutes after hemorrhage while the ALB deaths steadily occurred for up to 3

hours after hemorrhage.

The FFP deaths suddenly occurred in recovering animals after beginning the administration of a new FFP unit. We consider these deaths secondary to plasma incompatibility problems and/or vasoactive plasma factors. We speculate that even a minimal immunological reaction in severely hypovolemic swine could be lethal. If most of the swine deaths during treatment were immunologically related, then a compatible FFP treatment group should be associated with a better survival rate. Indeed 11 of 14 FFPx-treated swine survived. The 3 FFPx deaths that occurred were during or immediately after treatment. These deaths may have been due to antibodies undetected by our preliminary typing methods, vasoactive factors in improperly collected or thawed FFP units, the inherent mortality of the rapid hemorrhage model, or a combination of these reasons. Compatible FFP appeared to be almost as effective as WB in resuscitation of the severely hemorrhaged swine.

Volume expansion and tissue perfusion can be associated with survival in this study. The better survival of the WB group was associated with the highest AP, lowest HR, highest Hct, and lowest lactate values (Fig. 3A and B). The poorest survival of the NS group was associated with the lowest AP and a marginally decreased Hct (Fig. 3B). The crystalloid solution, NS, rapidly equilibrated to the interstitial space so that, by the end of treatment at 30 minutes after hemorrhage, the Hct stabilized between the Hct levels of WB and the other colloid solutions. This rapid equilibration of crystalloid solutions has been documented on numerous occasions since it was described adequately in man (6). ALB persisted in the intravascular space similar to FFP, as indicated by Hct. We do not know why the arterial lactate of the ALB group was elevated above all other groups at 30 and 60 minutes after hemorrhage (Fig. 3B). This observation remains unexplained.

Acid-base status also can be associated with survival. The best survival of the WB group is associated with one of the best recoveries of pH, HCO_3, and BE values to normal. The poor tissue perfusion and oxygen transport after NS led to metabolic acidosis, e.g., the lowest pH, HCO_3, and BE values during treatment and a higher lactate level than WB at the 30-minute period (Fig. 3B). The acid-base results might also be due, in part, to the acidifying effect of the increased chloride load of normal saline solutions as seen previously in this model (11) and in man (12). The increased percentage of chloride anions would quickly displace extracellular bicarbonate leading to plasma acidification. The low pH, HCO_3, and BE values during ALB treatment can be attributed, in part, to the increased chloride load of this solution as compared to WB or FFP (Table 2).

Besides offering better volume expansion and less chloride ions, WB and FFP were better buffer solutions than ALB or NS. The pH data in the FFP group paralleled the WB curve and were significantly

different from the NS or ALB groups at the 15- and 30-minute periods (Fig. 3C). At the 240- and 300-minute intervals the pH in surviving animals significantly favored all treatments over NS. The HCO_3 value at 300 minutes after hemorrhage in the surviving FFP group was significantly higher than the surviving NS, ALB, and even WB groups. FFP provides HCO_3 while NS and ALB do not. WB provides HCO_3 but not as much as an equal volume of FFP. BE at 300 minutes significantly favored FFP over WB. These data suggest that FFP is a better buffer solution than equal volumes of ALB. Indeed, swine or human FFP in vitro has over five times the buffer capacity of ALB and fifty times the buffer capacity of NS when these solutions are at pH 7.1 and 0.01 N HCl is added (13).

The immediate buffering capacity of the protein and HCO_3 in FFP is much more efficient than potential HCO_3 sources like lactate. In our swine model, lactate (from Ringer's lactate) is a minor source of HCO_3 compared to FFP but better than NS (11). Caution must be exercised when directly administering the HCO_3 of FFP during uncompensated acidosis - uncompensated alkalosis may result. A trend toward alkalosis after FFP is seen in our study. Hartmann and Senn (14) originally placed lactate in Ringer's solution to avoid the rapid changes in pH seen with HCO_3 administration.

The HR response of FFP, FFPx, and ALB, were consistently greater than WB from 240 to 1440 minutes after hemorrhage (Fig. 3A). The lower HR responses of WB suggest that oxygen requirements were being maintained better than the other groups that possessed a lower Hct and, therefore, oxygen carrying capacity (Fig. 3B). Initially pO_2 values at the end of hemorrhage increased from the before-hemorrhage values (Fig. 3E). The decline of pCO_2 was secondary to hyperventilation at the end of hemorrhage. Hypocapnia allowed the partial pressure of oxygen to fill a higher percentage of the total atmospheric pressure and partially accounts for an increase in pO_2 at the end of hemorrhage. However, as the pCO_2 and tachypnea returned to normal after hemorrhage, the pO_2 remained persistently elevated in the FFPx, NS, and ALB groups. We speculate that the pO_2 was lowered in the FFP and WB groups because of a ventilation-perfusion mismatch associated with particulate matter in WB or antigen-antibody complexes in the untyped FFP group. These possibilities, however, were not confirmed by autopsy findings in animals surviving for 3 days after hemorrhage.

The poor survival rates and lactic acidosis after the administration of human albumin to swine is interesting. The solution could have been antigenic. We feel this possibility is unlikely because hypotension relative to the WB and FFP groups was not seen during rapid administration. In addition the pO_2 decline seen with untyped FFP, presumably associated with an immunologic incompatibility, was not observed after ALB (Fig. 3E). The increased chloride load and the poor buffering capacity of ALB as compared to FFP are reasons why ALB is not a good agent for rapid resuscitation:

although ALB remains in the vascular space, as indicated by the low Hct level, this volume expansion is associated with a lactic acidosis unique to this solution.

WB is the best treatment for rapid hemorrhage because it provides volume, oxygen carrying capacity, and acid buffer in the form of bicarbonate and protein. As compared to NS, the lower chloride concentrations and necessary volumes of WB avoid administering an increased chloride load. Compatible FFP provides the best alternative to WB in this study because it incorporated all the advantages of WB except oxygen carrying capacity. However caution should be exercised when using FFP for rapid resuscitation. Although swine survived, we feel any further blood loss (rebleeding or surgery) would have been fatal in this situation of minimally adequate oxygen carrying capacity. This lesson of history was learned during World War II when the medical corps relied on plasma rather than hemorrhage control and WB administration (15). The great military advantage of lyophilized plasma lies in the fact that it can be used in situations where the procurement of blood is impractical. However, it appears unfortunate, after considering the results of this swine study, that plasma was abandoned in favor of albumin solutions, especially without considering a combination of the advantages for both types of colloid solutions. Another concern with the use of FFP is the immediate noncardiac pulmonary edema that has been associated with administration of this blood component. This reaction is thought to be anaphylactoid in etiology(16) and may have been due to imcompatible plasma and/or vasoactive substances. Frequently trauma patients receive rapid administration of FFP, crystalloid, and packed red cells during acute hypovolemia. When death occurs the etiology is thought to be the acute disease. Actually, the culprit may have been an FFP unit with insidious incompatibility or a minimal amount of activated vasoactive factors from FFP collected or administered outside of standard procedures. More commonly FFP is used in the treatment of diseases not involving hypovolemia. A deleterious response may not be noted during the treatment of these patients.

CONCLUSIONS

Compatible FFP is a better resuscitation agent than ALB to prevent death after an otherwise lethal hemorrhage. Although FFP and ALB are equal volume expanders in our swine model, FFP results in improved survival over ALB because it is a better acid buffer and contains less chloride.

RECOMMENDATIONS

Rapid resuscitation of acutely hypovolemic combat casualties should be accomplished with a solution having a buffering capacity and chloride concentration similar to plasma.

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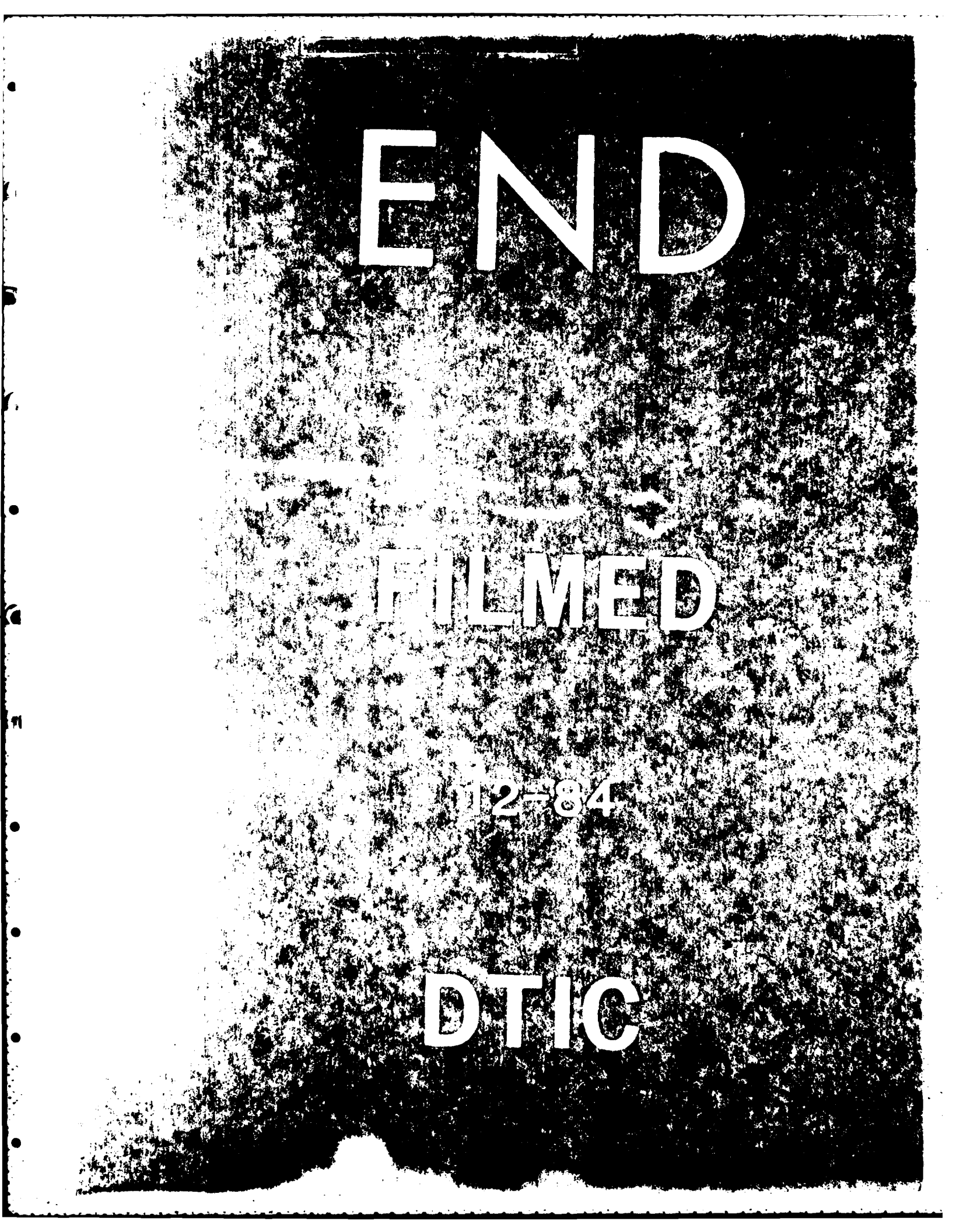
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